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Ischemia reperfusion injury in tumors: the role of oxygen radicals and nitric oxide.

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Oxidative stress is a key process involved in the action of several therapeutic modalities used in cancer treatment. Ischemia reperfusion insult provides a model system for investigating the processes involved in determining the sensitivity of tumor tissue to oxidative stress. We have investigated the response of the murine CaNT tumor to ischemia reperfusion injury and the role that oxygen radicals and nitric oxide may play in this phenomenon. Our results show that little or no cell kill is detected in tumors exposed to up to 3 h of ischemia if the tumors are excised immediately before reperfusion. However, if reperfusion is permitted, then extensive cell kill is evident 24 h later. i.v. administration of superoxide dismutase or catalase, at the time when vascular reperfusion occurred, resulted in a significant protection against tumor cell kill, suggesting that the damage was mediated by oxygen radicals. Conversely, administration of an inhibitor of nitric oxide synthase, N omega-nitro-L-arginine, resulted in potentiation of tumor cell damage. Administration of a nitric oxide (NO) donor, diethylamine NO, at the time when vascular reperfusion occurred resulted in significant protection against tumor damage. These results suggest that nitric oxide is a potent mediator in determining tumor damage after ischemia reperfusion injury. The role of intrinsic NO production by murine tumors was investigated by measuring the accumulation of nitrate in the medium of tumor explants cultured in vitro in two tumors with differing sensitivity to ischemia reperfusion damage. The clamp-insensitive tumor SaS showed a greater nitrate accumulation than the clamp-sensitive tumor CaNT, which may confer a greater capacity for preventing tumor and endothelial cell damage after oxidative stress.

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Metabolic and clonogenic consequences of ischaemia reperfusion insult in solid tumours.

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Tumour cell survival is intimately related to blood vessel function and so the tumour vasculature represents a novel target for cancer therapy. We have investigated a murine tumour model in which a metal clamp was used to occlude the vascular supply temporarily and then removed to allow reperfusion. This allows the study of ischaemia-reperfusion as a model system for investigating tumour response to metabolic and oxidative stress. Recent studies have shown that prolonged reduction of tumour blood flow results in a deterioration of the hypoxic and acidic microenvironment found within tumours which leads to cytotoxicity. This cytotoxicity is dramatically enhanced if these cells are subsequently reperfused. It was the aim of the present study to determine the relative contribution of cytotoxicity occurring during the ischaemic period and that occurring during reperfusion. Although significant reductions in tumour energy status were induced during the clamping period itself, these were poorly correlated with the degree of tumour cytotoxicity. Relative vascular perfusion, measured using a radiolabelled tracer, remained significantly depressed below the control value following clamp removal. The degree of recovery of perfusion was also dependent upon the clamp duration. Relative tumour perfusion at 1 h after clamp removal was 70.1 +/- 14.6 and 50.5 +/- 6.3% of control values after a 1 or 3 h clamp, respectively, and showed no significant further increase when measured at 24 h after clamp removal. Tumour cytotoxicity following ischaemia reperfusion insult was modulated by administering the anti-oxidant enzymes superoxide dismutase or catalase intravenously just before clamp removal. These enzymes are restricted to the vascular compartment, where it is proposed that they modulate the concentration of oxygen free radicals released during reperfusion and by neutrophil oxidative burst. Reperfusion injury to the tumour was enhanced by administration of an inhibitor of nitric oxide

synthase, nitro-L-arginine, probably owing to enhanced neutrophil adhesion and oxidative burst. Conversely, reperfusion injury to the tumour was reduced by administration of a nitric oxide donor, diethylamine nitric oxide. The murine model reported in this paper shows that ischaemia-reperfusion damage mediated by oxygen free radical formation provides a model system for investigating tumour response to oxidative stress at the level of the vascular endothelium.

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- Review, Tutorial

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